Materials Science and Engineering C 44 (2014) 352–361

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Controlled release of folic acid through liquid-crystalline folate nanoparticles

Rahul Misra [a], Henna Katyal [b], Sanat Mohanty [a,*]

[a] Advance Materials & Nanoscience Laboratory, Department of Chemical Engineering, Indian Institute of Technology-Delhi, HauzKhas, New Delhi 110016, India
[b] Department of Nanotechnology, Amity University, Noida, India

ARTICLE INFO

Article history:
Received 12 February 2014
Received in revised form 7 April 2014
Accepted 5 August 2014
Available online 12 August 2014

Keywords:
Chromonics
Folates
Cross-linking
Control release
Nanoparticles

ABSTRACT

The present study explores folate nanoparticles as nano-carriers for controlled drug delivery. Cross-linked nanoparticles of liquid crystalline folates are composed of ordered stacks. This paper shows that the folate nanoparticles can be made with less than 5% loss in folate ions. In addition, this study shows that folate nanoparticles can disintegrate in a controlled fashion resulting in controlled release of the folate ions. Release can be controlled by the size of nanoparticles, the extent of cross-linking and the choice of cross-linking cation. The effect of different factors like agitation, pH, and temperature on folate release was also studied. Studies were also carried out to show the effect of release medium and role of ions in the release medium on disruption of folate assembly.

1. Introduction

For patient compliance, drug delivery methods enhance the release profile, control absorption, and influence the bio-distribution of a drug administered to the body. Controlled drug delivery aims to release the drug at a specific site for enhanced and prolonged therapeutic effect as well as to maintain the level of therapeutic window to avoid re-administration. In conventional drug delivery methods, it is observed that the drug concentration in the blood varies with time between the maximum concentration (which may represent a toxic level) and a minimum value (below which the drug is ineffective). For example, in chemotherapy, both cancerous and non-cancerous cells are affected by chemotherapeutic agents due to their toxicity levels in the blood [1]. Conventional methods also have been seen to show lower retention and water solubility [2]. Specific distribution, reduced or no toxic effects and lower dosing are other advantages of controlled drug delivery. Thus, achieving a controlled release of drug is significant. Controlled release of drugs is desirable in chemotherapy, rheumatoid arthritis, asthmatic disorders, HIV, diabetes and several other auto-immune diseases.

Past studies have shown that it is feasible to target and release drugs at a predetermined site in a controlled manner [3,4]. Nano-carriers present several advantages in controlled drug delivery [5–7]. While numerous lab studies have shown the feasibility of nano-carrier based strategies, there are few clinically proven nanoparticle formulations that show controlled drug release [8–11]. Some successful strategies in the release of anti-cancer are listed in Table 1.

There remain some hurdles in controlled drug release with polymer and micellar based nanoparticles that have been extensively used in the past. The drug loss reported with these nano-carriers is in the range of 15–40% [12–15] — thus making this strategy wasteful and expensive. In addition, these nano-carriers are designed to carry drugs in "pockets" within the nanoparticle, thus resulting in "bursts".

Folate is a biocompatible, water soluble vitamin B which is found in green leafy vegetables, dried beans and peas (legumes) as well as citrus fruits and juices. It is essential for the formation of new cells and DNA inside the body. It is ingested by humans as a part of dietary supplements too. Higher amount of folic acid does not cause any harm as it is excreted through urine. Thus, there is lower risk of toxicity and side effects [20–22]. These advantages of folic acid provided strong motivation for using them as a nano-carrier for drug delivery. Fig. 1a represents the molecular structure of folic acid.

The present study explores the use of folate nanoparticles as nano-carriers with improved encapsulation and better controlled release. Folate molecules are seen to self-assemble (even at low concentrations) in ordered structures. Moreover, drugs and other guest molecules intercalate into the self-assembled structure resulting in ordered nanoparticles with the promise of better protection and better control of release. Unlike amphiphiles, their self-assemblies do not show any critical micelle concentration or optimum aggregation size and there is no Krafft temperature effect (seen in micelles) to regulate such assemblies [23–27].

* Corresponding author.
E-mail address: sanatm@chemical.iitd.ac.in (S. Mohanty).

http://dx.doi.org/10.1016/j.msec.2014.08.025
0928-4931/

Table 1
Strategies for controlled release of anti-cancer drugs through different nano-carriers.

Main drug/formulation	Type of nanoparticle	Release medium	Strategies/phenomenon of release	References
Highly porous nanocellulose aerogels	Cellulosic nano-carrier	Sodium dodecyl sulfate (SDS)	Interactions between the nanoparticles and the cellulose modulation of the matrix	[16]
Porous hollow silica nanoparticles	Silica nano-carrier	Simulated body fluid (SBF)	Entrapment of cefradine inside porous silica	[17]
PLGA–mPEG nanoparticles of Cisplatin	Polymer nanoparticle	Phosphate buffer saline (PBS)	In vitro nanoparticle degradation	[18]
Camptothecin–iron oxide nanoparticles	Magnetic nanoparticle	Dulbecco's modified Eagle's medium (DMEM)	Intracellular release of the Camptothecin molecules by an external magnetic stimulus	[19]

Past studies have shown that other guest molecules could be appropriately chosen to be part of the self-assembled folate liquid-crystalline solutions. These guests molecules generally interact with aromatic ring complexes to participate ordered self assemblies that form [28–38]. In addition, the nanoparticles formed from these liquid-crystalline solutions maintain the order. Hence, when the nanoparticles disintegrate, any guest molecules included in the assembly would also be released at the same rate as the folate molecules. This could result in better control of release compared to nanoparticles with shell–core like structures. While the inclusion of other molecules would somewhat change the release profile on the guest, understanding the baseline behavior of folic acid is necessary to design the release of drug from such nanoparticles. This article reports that folate based nanoparticles are model drug carriers that can be designed for long term sustained release with a high degree of control. These release rates can be controlled by the size and cross-linking of the particles, and by the nature of the release medium.

While past studies have explore the release of folates from other nano-carriers [40] or even the use of folate as a surface-modifying functional group [39], this is the first effort to develop folate nanoparticles as nano-carriers.

1.1. Folate nanoparticle design and release

An extensive study in the design of folate nanoparticles, thermodynamics of particle formation and characterization has been described elsewhere [41]. In brief, folate nanoparticles can be developed from liquid-crystalline folate solution by mixing it with HPMC (Hydroxy Propyl Methyl Cellulose) polymer and their size can be controlled by varying the relative concentrations of both components in the solution. HPMC is a water soluble cellulosic biocompatible polymer [42,43] used in the food industries as additives, emulsifier, and thickening and suspending agents. Fig. 1b represents the chemical structure of HPMC. In aqueous state, folate forms a two phase system with HPMC as folate ions with aromatic rings prefer to interact with themselves, rather than with HPMC.

Folates when mixed with HPMC get dispersed into nano-domains. This dispersion is exposed to aqueous solutions of multivalent salts to form stable nanoparticles. This process of dispersion also separates the HPMC from the folate nanoparticles. The multivalent cations exchange with the monovalent cations in the liquid crystalline solutions (NaOH in present case). The folate nano-domains cross-linked by multivalent cations are stable even in the absence of HPMC or when suspended in water. The cross-linking keeps the folate nanostructure stable intact.

When suspended in release medium consisting of sodium ions at about 0.8% by weight, the folate assembly is disrupted by exchange of an excess of sodium ions with the cross-linking multivalent ions in the

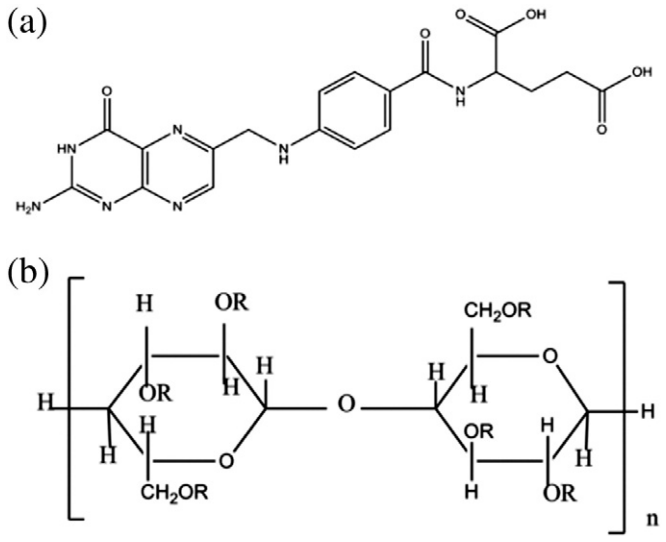

Fig. 1. Chemical structure of (a) folic acid and (b) HPMC polymer.

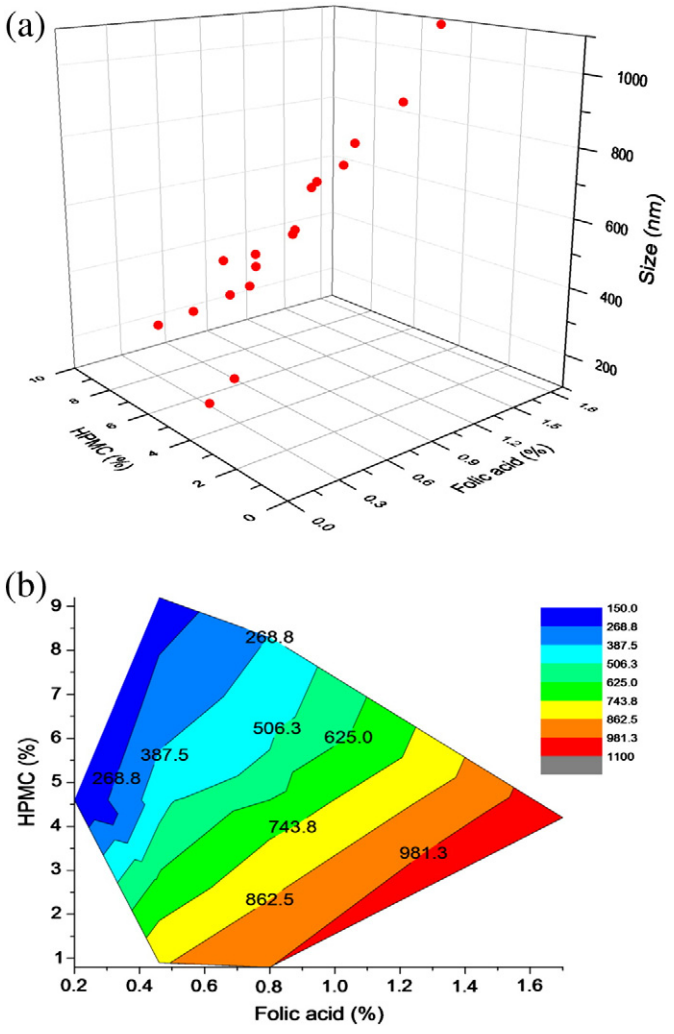

Fig. 2. Effect of relative concentration of folate and HPMC concentration on size distribution of folate nanoparticles. (a) Schematic representation. (b) Contour plot representation. By choosing the appropriate concentrations of both the compounds, folate nanoparticles of desirable size range can be developed.